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CHUGH, Anita [IN/IN]; RA-36, Inderpuri, New Delhi, Delhi 110012 (IN).

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(74) Common Representative: **RANBAXY LABORATORIES LIMITED**; c/o Deshmukh, Jay, R., 600 College Road East, Suite 2100, Princeton, NJ 08540 (US).

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(71) Applicant (for all designated States except US): **RANBAXY LABORATORIES LIMITED** [IN/IN]; 19, Nehru Place, New Delhi, Delhi 110019 (IN).

(71) Applicant and

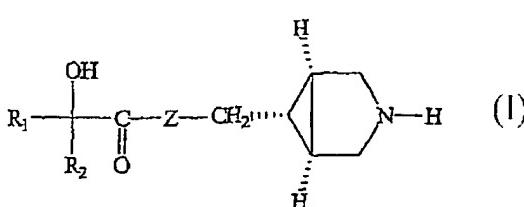
(72) Inventor: **KUMAR, Naresh** [IN/IN]; C-1796, Palam Vihar, Gurgaon, Haryana 122017 (IN).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **SALMAN, Mohammad** [IN/US]; 13 Hampshire Drive, Plainsboro, NJ 08536 (US). **SARMA, Pakala, Kumara, Savithru** [IN/IN]; 1091, 17b, Ifco Colony, Gurgaon, Haryana 122001 (IN). **DHARMARAJAN, Sankaranarayanan** [IN/IN]; Gurera House, 811, Sector 17a, Gurgaon, Haryana 122001 (IN).

A1

(54) Title: AZABICYCLO DERIVATIVES AS MUSCARINIC RECEPTOR ANTAGONISTS



receptors.

(57) Abstract: This invention generally relates to muscarinic receptor antagonists of formula(I) which are useful, among other uses, for the treatment of various diseases of the respiratory, urinary and gastrointestinal systems mediated through muscarinic receptors. Specifically, the invention relates to derivatives of azabicyclo compounds, including, for example, 6-substituted azabicyclo[3.1.0] hexanes, as well as pharmaceutical compositions containing such compounds and methods of treating diseases mediated through muscarinic

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## AZABICYCLO DERIVATIVES AS MUSCARINIC RECEPTOR ANTAGONISTS

Field of the Invention

This invention generally relates to muscarinic receptor antagonists which are  
5 useful, among other uses, for the treatment of various diseases of the respiratory, urinary  
and gastrointestinal systems mediated through muscarinic receptors. Specifically, the  
invention relates to derivatives of azabicyclo compounds, including, for example, 6-  
substituted azabicyclo[3.1.0] hexanes, as well as pharmaceutical compositions containing  
such compounds and methods of treating diseases mediated through muscarinic receptors.

10 Background of the Invention

Muscarinic receptors as members of the G Protein Coupled Receptors (GPCRs) are  
composed of a family of 5 receptor sub-types ( $M_1$ ,  $M_2$ ,  $M_3$ ,  $M_4$  and  $M_5$ ) and are activated  
by the neurotransmitter acetylcholine. These receptors are widely distributed on multiple  
organs and tissues and are critical to the maintenance of central and peripheral cholinergic  
15 neurotransmission. The regional distribution of these receptor sub-types in the brain and  
other organs has been documented. For example, the  $M_1$  subtype is located primarily in  
neuronal tissues such as cerebral cortex and autonomic ganglia, the  $M_2$  subtype is present  
mainly in the heart where it mediates cholinergically induced bradycardia, and the  $M_3$   
subtype is located predominantly on smooth muscle and salivary glands (*Nature*, 323,  
20 p.411 (1986); *Science*, 237, p.527 (1987)).

A review in *Current Opinions in Chemical Biology*, 3, p. 426 (1999), as well as in  
*Trends in Pharmacological Sciences*, 22, p. 409 (2001) by Eglen et. al., describes the  
biological potentials of modulating muscarinic receptor subtypes by ligands in different  
disease conditions, such as Alzheimer's Disease, pain, urinary disease condition, chronic  
25 obstructive pulmonary disease, and the like.

A review in *J. Med. Chem.*, 43, p. 4333 (2000), by Felder et. al. describes  
therapeutic opportunities for muscarinic receptors in the central nervous system and  
elaborates on muscarinic receptor structure and function, pharmacology and their  
therapeutic uses.

30 The pharmacological and medical aspects of the muscarinic class of acetylcholine  
agonists and antagonists are presented in a review in *Molecules*, 6, p. 142 (2001).

Birdsall et. al. in *Trends in Pharmacological Sciences*, 22, p. 215 (2001) have also summarized the recent developments on the role of different muscarinic receptor subtypes using different muscarinic receptor of knock out mice.

Muscarinic agonists such as muscarine and pilocarpine and antagonists such as atropine have been known for over a century, but little progress has been made in the discovery of receptor subtype-selective compounds, making it difficult to assign specific functions to the individual receptors. Although classical muscarinic antagonists such as atropine are potent bronchodilators, their clinical utility is limited due to high incidence of both peripheral and central adverse effects such as tachycardia, blurred vision, dryness of mouth, constipation, dementia, etc. Subsequent development of the quarterly derivatives of atropine such as ipratropium bromide are better tolerated than parenterally administered options, but most of these are not ideal anti-cholinergic bronchodilators, due to lack of selectivity for muscarinic receptor sub-types, resulting in dose-limiting side-effects such as thirst, nausea, mydriasis and those associated with the heart such as tachycardia mediated by the M<sub>2</sub> receptor.

*Annual Review of Pharmacological Toxicol.*, 41, p. 691 (2001), describes the pharmacology of the lower urinary tract infections. Although anti-muscarinic agents such as oxybutynin and tolterodine that act non-selectively on muscarinic receptors have been used for many years to treat bladder hyperactivity, the clinical effectiveness of these agents has been limited due to the side effects such as dry mouth, blurred vision and constipation. Tolterodine is considered to be generally better tolerated than oxybutynin. (Steers et. al., in *Curr. Opin. Invest. Drugs*, 2, 268; Chapple et. al., in *Urology*, 55, 33; Steers et al., Adult and Pediatric Urology, ed. Gillenwater et al., pp 1220-1325, St. Louis, MO; Mosby. 3<sup>rd</sup> edition (1996)).

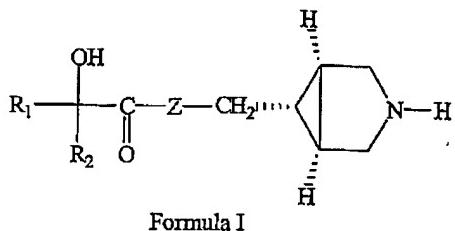
There remains a need for development of new highly selective muscarinic antagonists which can interact with distinct subtypes, thus avoiding the occurrence of adverse effects.

Compounds having antagonistic activity against muscarinic receptors have been described in Japanese patent application Laid Open Number 92921/1994 and 30 135958/1994; WO 93/16048; U.S. Patent No. 3,176,019; GB 940,540; EP 0325 571; WO 98/29402; EP 0801067; EP 038S054; WO 9109013; U.S. Patent No. 5,281,601. Also, U.S. Patent Nos. 6,174,900, 6,130,232 and 5,948,792; WO 97/45414 are related to

- 1,4-disubstituted piperidine derivatives; WO 98/05641 describes fluorinated, 1,4-disubstituted piperidine derivatives; WO 93/16018 and WO 96/33973 are other references of interest. US Patent No. 5,397,800 discloses 1-azabicyclo[2.2.1]heptanes. US Patent No. 5,001,160 describes 1-aryl-1-hydroxy-1-substituted-3-(4-substituted-1-piperazinyl)-2-propanones. WO 01/42213 describes 2-biphenyl-4-piperidinyl ureas. WO 01/42212 describes carbamate derivatives. WO 01/90081 describes amino alkyl lactam. WO 02/53564 describes novel quinuclidine derivatives. WO 02/00652 describes carbamates derived from arylalkyl amines. WO 02/06241 describes 1,2,3,5-tetrahydrobenzo(c)azepin-4-one derivatives.
- 10 A report in *J. Med. Chem.*, 44, p. 984 (2002), describes cyclohexylmethyl piperidinyl triphenylpropioamide derivatives as selective M<sub>3</sub> antagonist discriminating against the other receptor subtypes.
- Summary of the Invention
- In one aspect, azabicyclo derivatives, including, for example, 6-substituted azabicyclo[3.1.0]hexanes, 2,6- and 4,6-disubstituted derivatives and 2,4,6-trisubstituted derivatives are provided as muscarinic receptor antagonists which can be useful as safe and effective therapeutic or prophylactic agents for the treatment of various diseases of the respiratory, urinary and gastrointestinal systems. Also provided are processes for synthesizing such compounds.
- 15 20 In another aspect, pharmaceutical compositions containing such compounds are provided together with acceptable carriers, excipients or diluents which can be useful for the treatment of various diseases of the respiratory, urinary and gastrointestinal systems.
- The enantiomers, diastereomers, N-oxides, polymorphs, pharmaceutically acceptable salts and pharmaceutically acceptable solvates of these compounds as well as metabolites having the same type of activity are also provided, as well as pharmaceutical compositions comprising the compounds, their metabolites, enantiomers, diastereomers, 25 N-oxides, polymorphs, solvates or pharmaceutically acceptable salts thereof, in combination with a pharmaceutically acceptable carrier and optionally included excipients.
- 30 Other aspects will be set forth in the description which follows, and in part will be apparent from the description or may be learnt by the practice of the invention.

In accordance with one aspect, there are provided compounds having the structure of Formula I:

5



and their pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, metabolites, wherein

10 R<sub>1</sub> and R<sub>2</sub> are independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl or optionally substituted phenyl wherein optional substituent(s) can be selected from C<sub>1</sub>-C<sub>3</sub> alkyl, C<sub>1</sub>-C<sub>3</sub> alkoxy or halogen;

Z can represent oxygen or NR<sub>3</sub> wherein R<sub>3</sub> represents hydrogen or C<sub>1</sub>-C<sub>3</sub> alkyl.

15 In accordance with a second aspect, there is provided a method for treatment or prophylaxis of an animal or a human suffering from a disease or disorder of the respiratory, urinary and gastrointestinal systems, wherein the disease or disorder is mediated through muscarinic receptors. The method includes administration of at least one compound having the structure of Formula I.

20 In accordance with a third aspect, there is provided a method for treatment or prophylaxis of an animal or a human suffering from a disease or disorder associated with muscarinic receptors, comprising administering to a patient in need thereof, an effective amount of a muscarinic receptor antagonist compound as described above.

25 In accordance with a fourth aspect, there is provided a method for treatment or prophylaxis of an animal or a human suffering from a disease or disorder of the respiratory system such as bronchial asthma, chronic obstructive pulmonary disorders (COPD), pulmonary fibrosis, and the like; urinary system which induce such urinary disorders as urinary incontinence, lower urinary tract symptoms (LUTS), etc.; and gastrointestinal system such as irritable bowel syndrome, obesity, diabetes and gastrointestinal hyperkinesis with compounds as described above, wherein the disease or disorder is 30 associated with muscarinic receptors.

In accordance with a fifth aspect, there are provided processes for preparing the compounds as described above.

The compounds described herein exhibit significant potency in terms of their activity, as determined by *in vitro* receptor binding and functional assays and *in vivo* experiments using anaesthetized rabbits. The compounds that were found active *in vitro* were tested *in vivo*. Some of the compounds are potent muscarinic receptor antagonists with high affinity towards M<sub>3</sub> receptors. Therefore, pharmaceutical compositions for the possible treatment for the disease or disorders associated with muscarinic receptors are provided. In addition, the compounds can be administered orally or parenterally.

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#### Detailed Description of the Invention

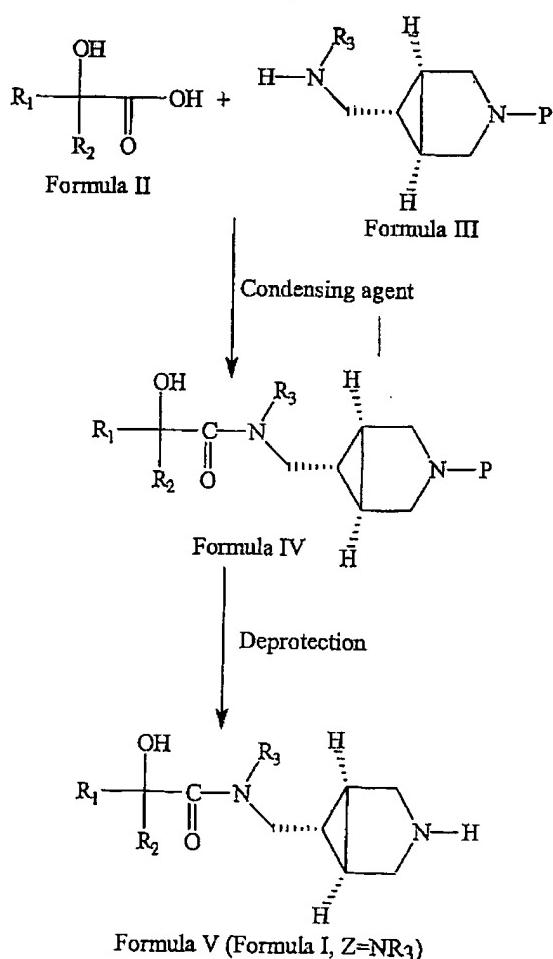
The compounds presented herein may be prepared by methods represented by the following reaction sequences as shown in Schemes I and II:

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Scheme I



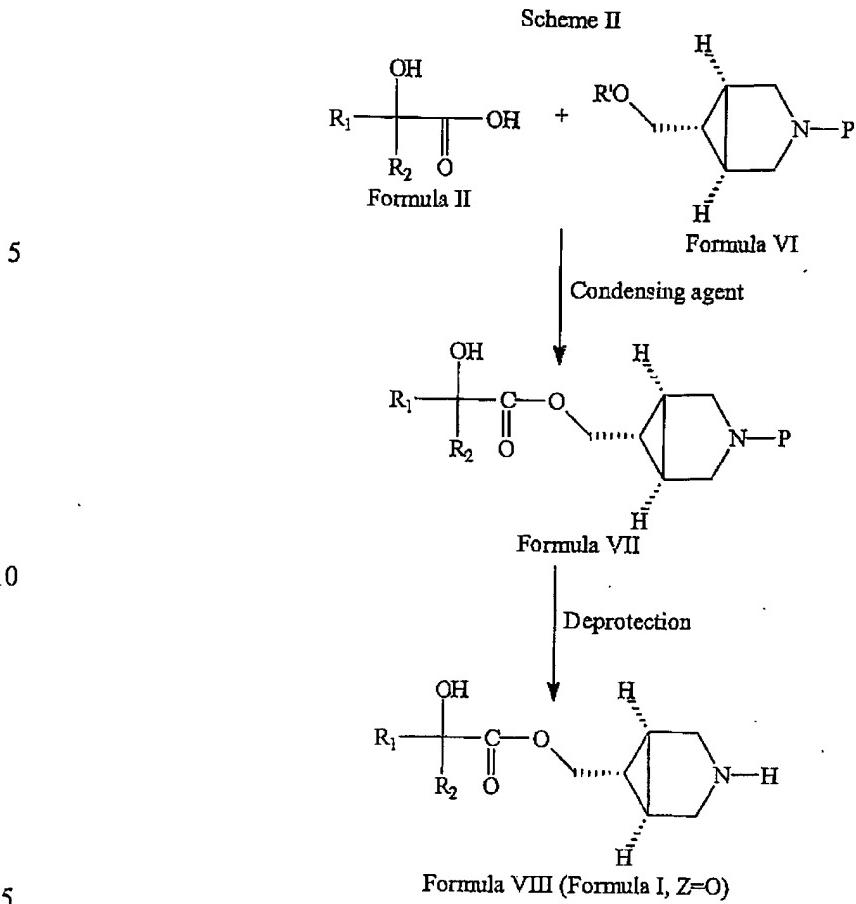
The compounds of Formula V may be prepared, for example, by the reaction sequence as shown in Scheme I. The preparation comprises reacting a compound of Formula II with a compound of Formula III, wherein

- R<sub>1</sub> and R<sub>2</sub> are independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl or  
5 optionally substituted phenyl wherein optional substituent(s) is/are selected from C<sub>1</sub>-C<sub>3</sub> alkyl, C<sub>1</sub>-C<sub>3</sub> alkoxy or halogen;

R<sub>3</sub> represents hydrogen or C<sub>1</sub>-C<sub>3</sub> alkyl and

P is any protecting group for an amino group, for example, benzyl or t-butyloxymethyl carbonyl groups.

- 10 The reaction between a compound of Formula II and a compound of Formula III can take place in the presence of N-methylmorpholine and 1-hydroxybenzotriazole and a condensing agent (for example, 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (EDC), 1,3-dicyclohexylcarbodiimide (DCC) or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)), in a solvent (such as N,N-dimethylformamide,
- 15 dimethylsulfoxide, toluene, xylene or chloroform, at temperatures ranging from about 0 to about 140°C), to give a protected compound of Formula IV which on deprotection in the presence of a deprotecting agent (for example, palladium on carbon and hydrogen, ammonium formate and palladium on carbon, trifluoroacetic acid (TFA) or hydrochloric acid) in an organic solvent (for example, methanol, ethanol, tetrahydrofuran or
- 20 acetonitrile, at temperatures ranging from about 10 to about 50°C) gives an unprotected compound of Formula V.



The compounds of Formula VIII may be prepared, for example, by the reaction sequence as shown in Scheme II. The preparation comprises reacting a compound of Formula II with a compound of Formula VI, wherein

R<sub>1</sub> and R<sub>2</sub> are independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl or optionally substituted phenyl wherein optional substituent(s) is/are selected from C<sub>1</sub>-C<sub>3</sub> alkyl, C<sub>1</sub>-C<sub>3</sub> alkoxy or halogen;

R' is any protecting group for hydroxy group, for example, p-toluene sulfonyl or methane sulfonyl and

P is any protecting group for an amino group, for example, benzyl or t-butyloxycarbonyl groups.

The reaction between a compound of Formula II and a compound of Formula VI can take place in the presence of a condensing agent (for example, 1,8-diazabicyclo[5.4.0]undecan-7-ene (DBU) or 1,4-diazabicyclo[2.2.2]octane (DABCO), in a

- solvent (such as benzene, toluene or xylene, at temperatures ranging from about 0 to about 140°C), to give a protected compound of Formula VII which on deprotection in the presence of a deprotecting agent (for example, palladium on carbon and hydrogen or ammonium formate and palladium on carbon) in an organic solvent (for example, 5 methanol or ethanol, at temperatures ranging from about 10 to about 50°C) gives an unprotected compound of Formula VIII.

In the above scheme, where specific bases, condensing agents, protecting groups, deprotecting agents, solvents, catalysts, temperatures, etc. are mentioned, it is to be understood that other bases, condensing agents, protecting groups, deprotecting agents, 10 solvents, catalysts, temperatures, etc. known to those skilled in the art may be used. Similarly, the reaction temperature and duration may be adjusted according to the desired needs.

Suitable salts of the compounds represented by the Formula I were prepared so as to solubilize the compound in aqueous medium for biological evaluations, as well as to be 15 compatible with various dosage formulations and also to aid in the bioavailability of the compounds. Examples of such salts include pharmacologically acceptable salts such as inorganic acid salts (for example, hydrochloride, hydrobromide, sulphate, nitrate and phosphate), organic acid salts (for example, acetate, tartarate, citrate, fumarate, maleate, tolounesulphonate and methanesulphonate). When carboxyl groups are included in the 20 Formula I as substituents, they may be present in the form of an alkaline or alkali metal salt (for example, sodium, potassium, calcium, magnesium, and the like). These salts may be prepared by various techniques, such as treating the compound with an equivalent amount of inorganic or organic, acid or base in a suitable solvent.

Particular compounds are shown here:

25 N-[(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-phenyl-2-hydroxy-2-(N-methyl) phenylacetamide (Compound No. 1);

N-[(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-phenyl-2-hydroxy-2-(N-methyl) phenylacetamide tartarate salt (Compound No. 2);

30 (2R, 2S)-N-[(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-isopropyl-2-hydroxy-2-phenylacetamide (Compound No. 3);

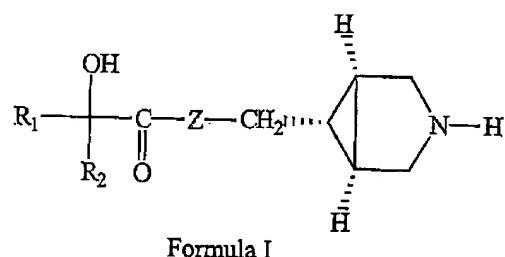
- (2R, 2S)-N-[(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-isopropyl-2-hydroxy-2-phenylacetamide hydrochloride salt (Compound No. 4);
- (2R, 2S)-N-[(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-(3-pentyl)-2-hydroxy-2-phenylacetamide (Compound No. 5);
- 5 (2R, 2S)-[(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-cyclopentyl-2-hydroxy-2-phenylacetic acid ester (Compound No. 6);
- (2R)-N-[(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-cyclopentyl-2-hydroxy-2-(N-methyl) phenylacetamide (Compound No. 7);
- (2R)-N-[(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-cyclopentyl-2-hydroxy-2-10 (N-methyl) phenylacetamide hydrochloride salt (Compound No. 8);
- (2R, 2S)-[(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-methyl-2-hydroxy-2-phenylacetic acid ester (Compound No. 9);
- (2R, 2S)-[(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-isopropyl-2-hydroxy-2-phenylacetic acid ester (Compound No. 10);
- 15 (2R, 2S)-[(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-(3-pentyl)-2-hydroxy-2-phenylacetic acid ester (Compound No. 11);
- (2R, 2S)-N-[(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-methyl-2-hydroxy-2-phenylacetamide (Compound No. 12);
- (2R)-N-[(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-isopropyl-2-hydroxy-2-(N-methyl) phenylacetamide (Compound No. 13);
- 20 (2R, 2S)-[(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-(m-methylphenyl)-2-hydroxy-2-phenylacetic acid ester (Compound No. 14);
- (2R, 2S)-N-[(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-(p-fluorophenyl)-2-hydroxy-2-phenylacetamide (Compound No. 15);
- 25 (2R, 2S)-N-[(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-(p-methylphenyl)-2-hydroxy-2-phenylacetamide (Compound No. 16);

(2R)-N-[(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-(p-fluorophenyl)-2-hydroxy-2-(N-methyl) phenylacetamide (Compound No. 17);

(2R)-N-[(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-(p-methylphenyl)-2-hydroxy-2-(N-methyl) phenylacetamide (Compound No. 18).

5

Table 1



Compound No.	R <sub>1</sub>	R <sub>2</sub>	Z
1	-C <sub>6</sub> H <sub>5</sub>	-C <sub>6</sub> H <sub>5</sub>	N-CH <sub>3</sub>
2 (tartarate salt)	-C <sub>6</sub> H <sub>5</sub>	-C <sub>6</sub> H <sub>5</sub>	N-CH <sub>3</sub>
3 (2R, 2S)	-C <sub>6</sub> H <sub>5</sub>	Isopropyl	NH-
4 (HCl salt) (2R, 2S)	-C <sub>6</sub> H <sub>5</sub>	Isopropyl	NH-
5 (2R, 2S)	-C <sub>6</sub> H <sub>5</sub>	3-pentyl	NH-
6 (2R, 2S)	-C <sub>6</sub> H <sub>5</sub>	Cyclopentyl	O
7 (2R, 2S)	-C <sub>6</sub> H <sub>5</sub>	Cyclopentyl	-N-CH <sub>3</sub>
8 (HCl salt) (2R, 2S)	-C <sub>6</sub> H <sub>5</sub>	Cyclopentyl	-N-CH <sub>3</sub>
9 (2R, 2S)	-C <sub>6</sub> H <sub>5</sub>	-CH <sub>3</sub>	O
10 (2R, 2S)	-C <sub>6</sub> H <sub>5</sub>	Isopropyl	O
11 (2R, 2S)	-C <sub>6</sub> H <sub>5</sub>	3-pentyl	O
12 (2R, 2S)	-C <sub>6</sub> H <sub>5</sub>	-CH <sub>3</sub>	NH-
13 (2R)	-C <sub>6</sub> H <sub>5</sub>	Isopropyl	-N-CH <sub>3</sub>
14 (2R, 2S)	-C <sub>6</sub> H <sub>5</sub>	m-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	O
15 (2R, 2S)	-C <sub>6</sub> H <sub>5</sub>	p-F-C <sub>6</sub> H <sub>4</sub>	NH-

16 (2R, 2S)	-C <sub>6</sub> H <sub>5</sub>	p-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	NH-
17 (2R)	-C <sub>6</sub> H <sub>5</sub>	p-F-C <sub>6</sub> H <sub>4</sub>	-N-CH <sub>3</sub>
18 (2R)	-C <sub>6</sub> H <sub>5</sub>	p-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	-N-CH <sub>3</sub>

- Because of their valuable pharmacological properties, the compounds described herein may be administered to an animal for treatment orally, or by a parenteral route.
- The pharmaceutical compositions described herein can be produced and administered in dosage units, each unit containing a certain amount of at least one compound described herein and/or at least one physiologically acceptable addition salt thereof. The dosage may be varied over extremely wide limits as the compounds are effective at low dosage levels and relatively free of toxicity. The compounds may be administered in the low micromolar concentration, which is therapeutically effective, and the dosage may be increased as desired up to the maximum dosage tolerated by the patient.

The compounds described herein can be produced and formulated as their enantiomers, diastereomers, N-Oxides, polymorphs, solvates and pharmaceutically acceptable salts, as well as metabolites having the same type of activity. Pharmaceutical compositions comprising the molecules of Formula I or metabolites, enantiomers, diastereomers, N-oxides, polymorphs, solvates or pharmaceutically acceptable salts thereof, in combination with pharmaceutically acceptable carrier and optionally included excipient can also be produced.

The examples mentioned below demonstrate general synthetic procedures, as well as specific preparations of particular compounds. The examples are provided to illustrate the details of the invention and should not be constrained to limit the scope of the present invention.

### Examples

Various solvents, such as acetone, methanol, pyridine, ether, tetrahydrofuran, hexanes, and dichloromethane, were dried using various drying reagents according to procedures described in the literature. IR spectra were recorded as nujol mulls or a thin neat film on a Perkin Elmer Paragon instrument. Nuclear Magnetic Resonance (NMR) were recorded on a Varian XL-300 MHz instrument using tetramethylsilane as an internal standard.

Example 1: Preparation of N-[(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-phenyl-2-hydroxy-2-(N-methyl) phenylacetamide (Compound No. 1)

**Step a: Synthesis of methane sulfonic acid 3-benzyl-3-azabicyclo[3.1.0]hex-6-yl-methyl ester**

5 To a solution of (3-benzyl-3-azabicyclo[3.1.0]hex-6-yl) methanol (prepared following *Synlett*, 1996; 1097) (5.2g, 25.6 mmole) in dichloromethane at 0°C triethylamine (10.6 mL, 76.8 mmole) and methane sulphonyl chloride (4 mL, 51.2 mmole) was added. It was gradually warmed to an ambient temperature and stirred for overnight. It was quenched by addition of saturated aqueous sodium bicarbonate solution and organic 10 layer was separated to give solution of crude product. This was washed with water, brine and dried over anhydrous sodium sulphate and the evaporated to give crude product. The crude product was purified by column chromatography using silica gel with hexane-triethylamine (99:1) as eluant to give the required product as pale yellow clear liquid (2.2 g, 30%).

15 **Step b: Synthesis of (3-benzyl-3-azabicyclo[3.1.0]hex-6-yl-methyl) methylamine**

To a solution of methane sulfonic acid 3-benzyl-3-azabicyclo[3.1.0]hex-6-yl-methyl ester

(2.4 g, 8.5 mmol) in methanol (20 ml) in a steel bomb, aqueous 40% methylamine solution (25 ml) was added. The steel bomb was tightened and warmed to 85-90°C for 20 about 15 hour. It was cooled down to an ambient temperature and then to -78°C and was opened up. The mixture was transferred to a round bottom flask and solvent was evaporated, diluted with water, dilute hydrochloric acid and extracted with ethyl acetate. Organic layer was separated and discarded. The aqueous layer was basified with 10% aqueous sodium hydroxide solution to pH 12-13. It was extracted with dichloromethane 25 and dried over anhydrous sodium sulphate. The filtered dichloromethane layer was evaporated to give the required compound as yellow liquid (1.8 g, 98%).

**Step c: Synthesis of N-[(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-3-benzyl-3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-phenyl-2-hydroxy-2-(N-methyl) phenylacetamide**

To a cold solution of benzillic acid (1.9 g, 8.33 mmol, commercially available) and 30 (3-benzyl-3-azabicyclo[3.1.0]hex-6-yl-methyl)methylamine (1.8 g, 8.33 mmol) in dimethylformamide (20 ml) at 0°C, N-methylmorpholine (1.8 mL, 16.6 mmol) and 1-

hydroxy benzotriazole (1.12 g, 8.33 mmol) were added and the mixture was stirred for about 45 min. To it 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.6 g, 8.33 mmol) was added and the mixture was gradually warmed to an ambient temperature and stirred for overnight. It was quenched by addition of water and compound was

5 extracted with ethyl acetate. The organic layer was separated and washed with water, brine and dried over anhydrous sodium sulphate. The organic layer was filtered and evaporated to give crude product. The crude product was purified by silica gel column chromatography using hexane-ethyl acetate (4:1 to 2:1) as eluant to give the required product as colourless sticky solid (1.3 g, 36%)

10 **Step d: Synthesis of N-[ $(1\alpha, 5\alpha, 6\alpha)$ -3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-phenyl-2-hydroxy-2-(N-methyl) phenylacetamide**

To a solution of N-[ $(1\alpha, 5\alpha, 6\alpha)$ -3-benzyl-3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-phenyl-2-hydroxy-2-(N-methyl) phenylacetamide (1.3g, 3.05mmole) in methanol (20 mL), catalyst palladium on carbon (10%, wet) was added and a 3-way hydrogenation tap fixed

15 with filled hydrogen balloon was fixed over it. The air was evacuated and purged with hydrogen. It was stirred for about 5 hours at an ambient temperature. The catalyst was filtered off over celite and washed with methanol. Filterate was evaporated to give the required product as colourless sticky liquid (0.95 g, 93%).

The compound exhibited a melting point of 72.4-73.7 °C. Infrared spectral data showed (DCM): 1627.9 cm<sup>-1</sup>. <sup>1</sup>H NMR spectral data showed (CDCl<sub>3</sub>): δ 8.42-8.29 (m, 10H), 4.52 (s, 2H), 4.17 (s, 2H), 3.94-4.00 (m, 3H), 3.58-3.64 (m, 4H), 2.45-2.58 (m, 2H), 1.91 (m, 1H). The mass spectrum showed peaks at m/e of: 337 (M+1).

Example 2: Preparation of N-[ $(1\alpha, 5\alpha, 6\alpha)$ -3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-phenyl-2-hydroxy-2-(N-methyl) phenylacetamide tartarate salt (Compound No. 2)

To a solution of N-[ $(1\alpha, 5\alpha, 6\alpha)$ -3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-phenyl-2-hydroxy-2-(N-methyl) phenylacetamide (0.933, 2.77mmole, prepared in Example 1, step d)) in ethanol (25 mL), L(+) tartaric acid (416 mg, 2.77mmole) was added and the solution was stirred for 1 hour at room temperature. A white precipitate appeared. It was

30 heated to 50-55 °C for 30 minutes and solvent was evaporated to half amount. Dry ether

was added to it and white precipitate was filtered off and washed with plenty of ether. The dry white powder was attained (1.3g, 96%).

The compound exhibited a melting point of 101-103 °C.

Similarly, the following compounds were prepared following the procedure  
5 described in Example 1.

(2R)-N-[(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-isopropyl-2-hydroxy-2-(N-methyl) phenylacetamide (Compound No. 13)

Infrared spectral data showed (DCM): 1619.7 cm<sup>-1</sup>. <sup>1</sup>HNMR spectral data showed (D<sub>2</sub>O):  $\delta$  7.25-7.45 (m, 5H), 3.45-3.51 (m, 1H), 2.80-2.83 (m, 6H), 1.94-1.96 (brs, 3H),  
10 1.24-1.33 (m, 3H), 0.86-0.98 (m, 6H). The mass spectrum showed peaks at m/e of: 303 (M+H).

(2R)-N-[(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-(p-fluorophenyl)-2-hydroxy-2-(N-methyl) phenylacetamide (Compound No. 17)

<sup>1</sup>HNMR spectral data showed (CDCl<sub>3</sub>):  $\delta$  7.36-7.04 (m, 9H), 3.49-3.43 (m, 2H),  
15 3.08-2.60 (m, 8H), 1.40-1.36 (m, 2H), 1.24-1.33 (m, 3H), 0.86-0.98 (m, 6H). The mass spectrum showed peaks at m/e of: 303 (M+H).

(2R)-N-[(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-(p-methylphenyl)-2-hydroxy-2-(N-methyl) phenylacetamide (Compound No. 18)

<sup>1</sup>HNMR spectral data showed (DMSO):  $\delta$  7.46-7.33 (m, 5H), 4.59 (s, 2H), 3.54-  
20 3.46 (m, 10H), 3.17-3.05 (m, 3H), 1.36-1.28 (m, 2H).

(2R)-N-[(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-cyclopentyl-2-hydroxy-2-(N-methyl) phenylacetamide (Compound No. 7)

Example 3: (2R)-N-[(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-cyclopentyl-2-hydroxy-2-(N-methyl) phenylacetamide hydrochloride salt (Compound No. 8)

To a solution of (2R)-N-[(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-cyclopentyl-2-hydroxy-2-(N-methyl) phenylacetamide in dichloromethane (14.0 mL), ethanolic hydrochloride (3.5 N, 2.1 mL) was added at 0-5 °C and stirred for about 30 minutes at 20-25 °C. The solvent was removed under reduced pressure and the residue was

triturated with n-hexane to get a solid. The solid so obtained was filtered and washed with hexane and dried under vacuum to get the dried product in 90.1 yield.

Infrared spectral data showed (DCM): 1617.6 cm<sup>-1</sup>. <sup>1</sup>HNMR spectral data showed  
5 (D<sub>2</sub>O) : δ 7.45-7.52 (m, 5H), 3.42-3.50 (m, 4H), 3.22-3.29 (m, 2H), 2.90 (s, 3H), 1.80 (m,  
1H), 1.40-1.50 (m, 8H), 1.22-1.27 (m, 2H), 1.10 (m, 1H). The mass spectrum showed  
peaks at m/e of: 329 (M+H).

Example 4: Preparation of (2R, 2S)-N-[(1α, 5α, 6α)-3-azabicyclo[3.1.0]hex-6-yl-methyl]-  
10 2-isopropyl-2-hydroxy-2-phenylacetamide (Compound No. 3)

**Step a: Synthesis of (3-benzyl-3-azabicyclo[3.1.0]hex-6-yl-methyl) amine**

This compound was synthesized following the procedure described in EP 0413  
455.

**Step b: Synthesis of N-[(1α, 5α, 6α)-3-benzyl-3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-  
15 isopropyl-2-hydroxy-2-phenylacetamide**

To a cold solution of 2-isopropyl-2-hydroxy-2-phenylacetic (prepared following *J.  
Amer. Chem. Soc.*, 1953; 75: 2654 and *J. Org. Chem.*, 2000; 65:6283) (1.9 g, 8.33 mmol,) and (3-benzyl-3-azabicyclo[3.1.0]hex-6-yl-methyl)amine (prepared following the  
procedure described in EP 0413455) (1.8 g, 8.33 mmol) in dimethylformamide (20 ml) at  
20 0°C, N-methylmorpholine (1.8 ml, 16.6 mmol) and 1-hydroxy benzotriazole (1.12 g, 8.33  
mmol) were added and the mixture was stirred for about 45 min. To it 1-(3-  
dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.6 g, 8.33 mmol) was added  
and the mixture was gradually warmed to an ambient temperature and stirred for  
overnight. It was quenched by addition of water and compound was extracted with ethyl  
25 acetate. The organic layer was separated and washed with water, brine and dried over  
anhydrous sodium sulphate. The organic layer was filtered and evaporated to give crude  
product. The crude product was purified by silica gel column chromatography using  
hexane-ethyl acetate (4:1 2:1) as eluant.

**Step c: Synthesis of (2R, 2S)-N-[(1α, 5α, 6α)-3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-  
30 isopropyl-2-hydroxy-2-phenylacetamide**

To a solution of N-[ $(1\alpha, 5\alpha, 6\alpha)$ -3-benzyl-3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-isopropyl-2-hydroxy-2-phenylacetamide (1.3g, 30.5mmole) in dry methanol (25.0 mL), 5% palladium on carbon (0.2 g), (50% wet) was added under nitrogen. Then anhydrous ammonium formate (0.8 g, 12.38 mmole) was added under stirring and the reaction mixture was refluxed for half an hour under nitrogen atmosphere. Cooled to room temperature and the reaction mixture was filtered through a bed of hyflo. The hyflo bed was washed with methanol (75.0 mL), ethyl acetate (25.0 mL) and water (25.0 mL). The filterate was concentrated under vaccum. The residue was diluted with water and pH of the resulting solution was adjusted to (pH~14) with 1N NaOH. Extracted with ethyl acetate (2x50 mL) and the ethyl acetate layer was washed with water and brine solution. Dried over anhydrous sodium sulphate and concentrated to give the title compound.

Infrared spectral data showed (DCM): 1654 cm<sup>-1</sup>. <sup>1</sup>HNMR spectral data showed (CDCl<sub>3</sub>): δ 7.60-7.62 (m, 2H), 7.24-7.37 (m, 3H), 6.74 (s, 1H), 3.06-3.16 (m, 2H), 2.79-2.94 (m, 5H), 1.26-1.31 (m, 2H), 1.00 (d, J=6Hz, 3H), 0.72-0.77 (m, 4H). The mass spectrum showed peaks at m/e of: 289 (M+1).

Example 5: Preparation of (2R, 2S)-N-[ $(1\alpha, 5\alpha, 6\alpha)$ -3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-isopropyl-2-hydroxy-2-phenylacetamide hydrochloride salt (Compound No. 4)

To a solution of (2R or 2S)-N-[ $(1\alpha, 5\alpha, 6\alpha)$ -3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-isopropyl-2-hydroxy-2-phenylacetamide (1.4 g, 4.9 mmole) in dichloromethane (14.0 mL), etahnolic hydrochloride (3.5 N, 2.1 mL, 7.3 mmole) was added at 0-5 °C and stirred for about 30 minutes at 20-25 °C. The solvent was removed under reduced pressure and the residue was triturated with n-hexane to get a solid. The solid so obtained was filtered and washed with hexane and dried ubder vacuum to get the dried product in 95.1 (1.5 g) yield.

The compound exhibited a melting point of 70 °C (softening start). Infrared spectral data showed (DCM): 1641.1 cm<sup>-1</sup>. <sup>1</sup>HNMR spectral data showed (CDCl<sub>3</sub>): δ 7.63-7.65 (m, 2H), 7.40-7.47 (m, 3H), 3.30-3.37 (m, 4H), 3.14-3.16 (m, 2H), 2.90-2.93 (m, 1H), 1.74 (s, 2H), 1.21-1.23 (m, 1H), 1.00-1.01 (m, 3H), 0.81-0.83 (m, 3H).

Similarly, the following compounds were prepared following the procedure described in Example 4.

(2R, 2S)-N-[(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-(3-pentyl)-2-hydroxy-2-phenylacetamide (Compound No. 5)

Infrared spectral data showed (DCM): 1651.7 cm<sup>-1</sup>. <sup>1</sup>HNMR spectral data showed (CDCl<sub>3</sub>):  $\delta$  7.61-7.64 (m, 2H), 7.27-7.35 (m, 3H), 6.83 (s, 1H), 2.83-3.16 (m, 7H), 2.35 (m, 2H), 1.90-2.00 (m, 1H), 0.78-1.47 (m, 14H). The mass spectrum showed peaks at m/e of: 317 (M+1)

(2R, 2S)-N-[(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-methyl-2-hydroxy-2-phenylacetamide (Compound No. 12)

Infrared spectral data showed (DCM): 1655.5 cm<sup>-1</sup>. <sup>1</sup>HNMR spectral data showed (CDCl<sub>3</sub>):  $\delta$  7.54-7.56 (m, 2H), 7.28-7.37 (m, 3H), 6.76 (brs, 1H), 3.05-3.20 (m, 2H), 2.80-2.93 (m, 4H), 1.79 (s, 3H), 1.22-1.32 (m, 2H), 0.76-0.80 (m, 1H). The mass spectrum showed peaks at m/e of: 261(M+1).

(2R, 2S)-N-[(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-(p-fluorophenyl)-2-hydroxy-2-phenylacetamide (Compound No. 15)

15       <sup>1</sup>HNMR spectral data showed (CDCl<sub>3</sub>):  $\delta$  7.45-7.03 (m, 9H), 6.70 (brs, 1H), 3.26-3.22 (m, 2H), 2.96-2.83 (m, 4H), 1.34-1.30 (m, 3H). The mass spectrum showed peaks at m/e of: 341.39 (M+1)

(2R, 2S)-N-[(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-(p-methylphenyl)-2-hydroxy-2-phenylacetamide (Compound No. 16)

20       <sup>1</sup>HNMR spectral data showed (CDCl<sub>3</sub>):  $\delta$  7.44-7.14 (m, 9H), 6.70 (brs, 1H), 3.25-3.21 (m, 2H), 2.97-2.84 (m, 4H), 2.39-2.29 (m, 3H), 1.30-1.28 (m, 3H). The mass spectrum showed peaks at m/e of: 337.40 (M+1).

Example 6: Preparation of (2R, 2S)-[(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-cyclopentyl-2-hydroxy-2-phenylacetic acid ester (Compound No. 6)

**Step a: Synthesis of [(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-3-benzyl-3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-cyclopentyl-2-hydroxy-2-phenylacetic acid ester**

To a cold solution of 2-cyclopentyl-2-hydroxy-2-phenylacetic acid (1.9 g, 8.33 mmol) (prepared following *J. Amer. Chem. Soc.*, 1953; 75: 2654 and *J. Org. Chem.*, 2000; 65:6283) and methane sulfonic acid 3-benzyl-3-azabicyclo[3.1.0]hex-6-yl-methyl ester

(prepared in Example 1, step a) (2.4 g, 8.5 mmol) in dimethylformamide (20 ml) at 0°C, 1,8-diazabicyclo[5.4.0]undecan-7-ene (DBU) (1.6 g, 8.33 mmol) was added and the mixture was gradually warmed to an ambient temperature and stirred for overnight. It was quenched by addition of water and compound was extracted with ethyl acetate. The 5 organic layer was separated and washed with water, brine and dried over anhydrous sodium sulphate. The organic layer was filtered and evaporated to give crude product. The crude product was purified by silica gel column chromatography.

**Step b: Synthesis of [(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-cyclopentyl-2-hydroxy-2-phenylacetic acid ester**

10 To a solution of [(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-3-benzyl-3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-cyclopentyl-2-hydroxy-2-phenylacetic acid ester in dry methanol (25.0 mL), 5% palladium on carbon (0.2 g), (50% wet) was added under nitrogen. Then anhydrous ammonium formate (0.8 g, 12.38 mmole) was added under stirring and the reaction mixture was refluxed for half an hour under nitrogen atmosphere. Cooled to room temperature and the 15 reaction mixture was filtered through a bed of hyflo. The hyflo bed was washed with methanol (75.0 mL), ethyl acetate (25.0 mL) and water (25.0 mL). The filtrate was concentrated under vacuum. The residue was diluted with water and pH of the resulting solution was adjusted to (pH~14) with 1N NaOH. Extracted with ethyl acetate (2x50 mL) and the ethyl acetate layer was washed with water and brine solution. Dried over 20 anhydrous sodium sulphate and concentrated to give the title compound.

$^1\text{H}$ NMR spectral data showed ( $\text{CDCl}_3$ ):  $\delta$  7.67-7.64 (m, 2H), 7.36-7.28 (m, 3H), 4.13-4.05 (m, 2H), 2.97-2.86 (m, 4H), 2.29-1.50 (m, 12H). The mass spectrum showed peaks at m/e of: 316.31 (M+1).

Similarly, the following compounds were prepared following the procedure 25 described in Example 6.

(2R, 2S)-[(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-methyl-2-hydroxy-2-phenylacetic acid ester (Compound No. 9)

Infrared spectral data showed (DCM): 1729.7  $\text{cm}^{-1}$ .  $^1\text{H}$ NMR spectral data showed (CDCl<sub>3</sub>):  $\delta$  7.55-7.58 (m, 2H), 7.29-7.38 (m, 3H), 4.02-4.12 (m, 2H), 2.82-2.94 (m, 4H), 30 1.71 (s, 3H), 1.48 (s, 2H), 0.93-0.97 (m, 1H). The mass spectrum showed peaks at m/e of: 262 (M+1).

(2R, 2S)-[(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-isopropyl-2-hydroxy-2-phenylacetic acid ester (Compound No. 10)

Infrared spectral data showed (DCM): 1723.8 cm<sup>-1</sup>. <sup>1</sup>HNMR spectral data showed (CDCl<sub>3</sub>):  $\delta$  7.65-7.67 (m, 2H), 7.24-7.37 (m, 3H), 4.05-4.16 (m, 2H), 2.81-2.93 (m, 4H), 5 2.61-2.66 (m, 1H), 1.29-1.39 (m, 3H), 0.94-1.02 (m, 3H), 0.71 (d, J=6Hz, 2H). The mass spectrum showed peaks at m/e of: 290 (M+1).

(2R, 2S)-[(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-(3-pentyl)-2-hydroxy-2-phenylacetic acid ester (Compound No. 11)

Infrared spectral data showed (DCM): 1721.4 cm<sup>-1</sup>. <sup>1</sup>HNMR spectral data showed 10 (CDCl<sub>3</sub>):  $\delta$  7.64-7.67 (m, 2H), 7.29-7.37 (m, 3H), 4.02-4.11 (m, 2H), 2.92-3.02 (m, 4H), 2.15-2.19 (m, 1H), 1.42-1.51 (m, 4H), 1.09-1.29 (m, 3H), 0.98-1.03 (m, 3H), 0.71-0.76 (m, 3H). The mass spectrum showed peaks at m/e of: 318 (M+1).

(2R, 2S)-[(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-(m-methylphenyl)-2-hydroxy-2-phenylacetic acid ester (Compound No. 14)

15 <sup>1</sup>HNMR spectral data showed (CDCl<sub>3</sub>):  $\delta$  7.43-7.12 (m, 14H), 4.18-4.16 (m, 2H), 3.03-2.91 (m, 4H), 2.33-2.28 (m, 3H), 1.30-1.28 (m, 3H). The mass spectrum showed peaks at m/e of: 338.34 (M+1).

Biological Activity

20 **Radioligand Binding Assays:** The affinity of test compounds for M<sub>2</sub> and M<sub>3</sub> muscarinic receptor subtypes was determined by [<sup>3</sup>H]-N-methylscopolamine binding studies, using rat heart and submandibular gland, respectively, as described by Moriya et al., (Life Sci., 1999; 64(25):2351-2358) with minor modifications as follows. The membrane preparation was done with the following modifications: a low spin step of 500g for 10 minutes at 4°C was used; the buffer was 20 mM HEPES, 10 mM EDTA, at pH 7.4; the high speed spin was done at 40,000g and the homogenate was passed through a filter gauge before any spinning. The assay conditions were modified as follows: the assay volume was 250  $\mu$ L; the incubation time was 3 hours; the PE concentration was 0.1%; the filtermat used was GF/B from Wallac; the scintillant used was Supermix from Wallac; the 25 amount of scintillant was 500  $\mu$ L/well; and the counter used was a 1450 microbeta PLUS, from Wallac.

30

**Membrane preparation:** Submandibular glands and heart were isolated and placed in ice cold homogenising buffer (HEPES 20mM, 10mM EDTA, pH 7.4) immediately after sacrifice. The tissues were homogenised in 10 volumes of homogenising buffer and the homogenate was filtered through two layers of wet gauze and filtrate was centrifuged at 5 500g for 10min. The supernatant was subsequently centrifuged at 40,000g for 20 min. The pellet thus obtained was resuspended in same volume of assay buffer (HEPES 20 mM, EDTA 5mM, pH 7.4) and were stored at -70°C until the time of assay.

**Ligand binding assay:** The compounds were dissolved and diluted in DMSO. The 10 membrane homogenates (150-250 µg protein) were incubated in 250 µl of assay buffer (HEPES 20 mM, pH 7.4) at 24-25°C for 3h. Non-specific binding was determined in the presence of 1 µM atropine. The incubation was terminated by vacuum filtration over GF/B fiber filters (Wallac). The filters were then washed with ice cold 50mM Tris HCl buffer (pH 7.4). The filter mats were dried and bound radioactivity retained on filters was 15 counted. The IC<sub>50</sub> and K<sub>d</sub> were estimated by using the non-linear curve fitting program using G Pad Prism software. The value of inhibition constant K<sub>i</sub> was calculated from competitive binding studies by using Cheng & Prusoff equation (*Biochem Pharmacol*, 1973; 22:3099-3108), K<sub>i</sub> = IC<sub>50</sub> / (1+L/K<sub>d</sub>), where L is the concentration of [<sup>3</sup>H]NMS used in the particular experiment. pK<sub>i</sub> = -[log K<sub>i</sub>].

20 The Ki results of the compounds observed were in the range of 0.05 nM to 136 nM for M<sub>3</sub> receptor and 0.06 nM to 34.6 nM for M<sub>2</sub> receptor.

#### **Functional Experiments using isolated rat bladder:**

**Methodology:** Animals are euthanized by overdose of urethane and the whole bladder is 25 isolated and removed rapidly and placed in ice cold Tyrode buffer with the following composition (mMol/L) NaCl 137; KC1 2.7; CaCl<sub>2</sub> 1.8; MgCl<sub>2</sub> 0.1; NaHCO<sub>3</sub> 11.9; NaH<sub>2</sub>PO<sub>4</sub> 0.4; glucose 5.55 and continuously gassed with 95% O<sub>2</sub> and 5 % CO<sub>2</sub>.

The bladder is cut into longitudinal strips (3mm wide and 5-6 mm long) and mounted in 10 ml organ baths at 30° C, with one end connected to the base of the tissue 30 holder and the other end connected to a polygraph through a force displacement transducer. Each tissue is maintained at a constant basal tension of 2 g and allowed to

equilibrate for 1 hour during which the PSS is changed every 15 min. At the end of the equilibration period, the stabilization of the tissue contractile response is assessed with 1  $\mu$ mol/L of Carbachol consecutively, 2-3 times. Subsequently a cumulative concentration response curve to carbachol ( $10^{-9}$  mol/L to  $3 \times 10^{-5}$  mol/L) is obtained. After several  
5 washes, once the baseline is achieved, cumulative concentration response curve is obtained in presence of NCE (NCE added 20 min. prior to the second CRC).

The contractile results are expressed as % of control E max. ED<sub>50</sub> values are calculated by fitting a non-linear regression curve (Graph Pad Prism). The pKB values are calculated by the formula pKB = - log [ (molar concentration of antagonist/ (dose ratio-  
10 1))] where, dose ratio = ED<sub>50</sub> in the presence of antagonist/ED<sub>50</sub> in the absence of antagonist.

***In vivo experiments using anesthetized rabbit:*** The effect of test substances was studied on carbachol evoked changes on bladder pressure, heart rate and salivation.

15 Male rabbits weighing 1.2-3 kg were anaesthetized with urethane (1.5g/kg), and administered as a slow intravenous infusion through the marginal ear vein. The tracheae were cannulated to maintain airway patency. Blood pressure was recorded from the femoral artery by means of a Statham P10 EZ pressure transducer connected to a Grass model 7D polygraph. The heart rate was monitored by a tachograph triggered by the pulse  
20 wave of blood pressure. The other femoral artery was cannulated for the administration of carbachol. Test compound and saline were infused intravenously via the femoral vein.

The bladder was exposed through a midline laparotomy and both the ureters were identified, carefully separated and ligated. The ureters were incised proximally to allow free flow of urine from the kidney to the exterior. Bladder neck was gently held and the  
25 urethra was traced and separated from the adjoining tissues. PE canula was introduced into the bladder and ligated. The bladder was drained and subsequently filled with 15ml of warm saline (37°C). The other end of the intravesical catheter was connected to the Grass model 7D polygraph through a Statham P10 EZ pressure transducer to monitor the bladder pressure. Care was taken to keep the exposed area moist and warm. A period of  
30 30-60 min was allowed for stabilization of parameters subsequent to surgery. Salivation response was assessed by placing preweighed absorbent cotton gauze in the buccal cavity for 2 minutes after carbachol administration.

The effect of the compound on carbachol ( $1.5\mu\text{g}/\text{kg}$ , intrarterial) induced changes on blood pressure, heart rate and bladder pressure were observed. At least two stable responses were obtained. These responses were considered as 100%. Subsequently, effect of increasing dose of test compound or vehicle (i.v, 12 to 15 min before carbachol  
5 challenge) was studied.

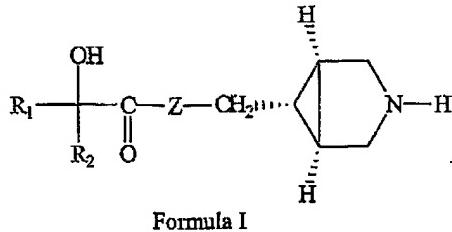
The change in bladder pressure, salivation and agonist induced bradycardia were expressed as % change from pretreatment control.  $\text{ID}_{50}$  values (dose required to inhibit 50% of response) were calculated from non-linear curve fitting for sigmoidal dose response curve using Graph Pad Prism software and values were expressed as  $\mu\text{g}/\text{kg}$ . The  
10  $\text{ID}_{50}$  values for bladder pressure for compounds tested ranged from about 1.89 to about 4.2  $\mu\text{g}/\text{kg}$ . The  $\text{ID}_{50}$  values for salivation for compounds tested ranged from about 3.7 to / about 30.4  $\mu\text{g}/\text{kg}$ .

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the  
15 art and are intended to be included within the scope of the present invention.

## WE CLAIM

1. Compounds having the structure of Formula I:

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and their pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, or metabolites, wherein R<sub>1</sub> and R<sub>2</sub> are independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl or optionally substituted phenyl wherein optional substituent(s) is/are selected from C<sub>1</sub>-C<sub>3</sub> alkyl, C<sub>1</sub>-C<sub>3</sub> alkoxy and halogen;  
Z represents oxygen or NR<sub>3</sub> wherein R<sub>3</sub> represents hydrogen or C<sub>1</sub>-C<sub>3</sub> alkyl.

2. A compound selected from

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N-[(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-phenyl-2-hydroxy-2-(N-methyl) phenylacetamide (Compound No. 1);

N-[(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-phenyl-2-hydroxy-2-(N-methyl) phenylacetamide tartarate salt (Compound No. 2);

(2R, 2S)-N-[(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-isopropyl-2-hydroxy-2-phenylacetamide (Compound No. 3);

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(2R, 2S)-N-[(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-isopropyl-2-hydroxy-2-phenylacetamide hydrochloride salt (Compound No. 4);

(2R, 2S)-N-[(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-(3-pentyl)-2-hydroxy-2-phenylacetamide (Compound No. 5);

25

(2R, 2S)-[(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-cyclopentyl-2-hydroxy-2-phenylacetic acid ester (Compound No. 6);

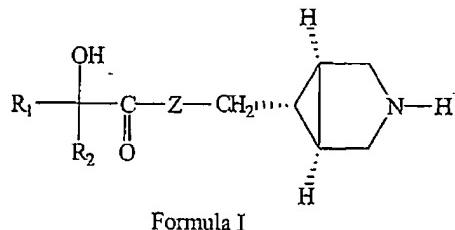
(2R)-N-[(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-cyclopentyl-2-hydroxy-2-(N-methyl) phenylacetamide (Compound No. 7);

(2R)-N-[(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-cyclopentyl-2-hydroxy-2-(N-methyl) phenylacetamide hydrochloride salt (Compound No. 8);

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(2R, 2S)-[(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-methyl-2-hydroxy-2-phenylacetic acid ester (Compound No. 9);

- (2R, 2S)-[(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-isopropyl-2-hydroxy-2-phenylacetic acid ester (Compound No. 10);
- (2R, 2S)-[(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-(3-pentyl)-2-hydroxy-2-phenylacetic acid ester (Compound No. 11);
- 5 (2R, 2S)-N-[(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-methyl-2-hydroxy-2-phenylacetamide (Compound No. 12);
- (2R)-N-[(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-isopropyl-2-hydroxy-2-(N-methyl) phenylacetamide (Compound No. 13);
- 10 (2R, 2S)-[(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-(m-methylphenyl)-2-hydroxy-2-phenylacetic acid ester (Compound No. 14);
- (2R, 2S)-N-[(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-(p-fluorophenyl)-2-hydroxy-2-phenylacetamide (Compound No. 15);
- (2R, 2S)-N-[(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-(p-methylphenyl)-2-hydroxy-2-phenylacetamide (Compound No. 16);
- 15 (2R)-N-[(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-(p-fluorophenyl)-2-hydroxy-2-(N-methyl) phenylacetamide (Compound No. 17);
- (2R)-N-[(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-3-azabicyclo[3.1.0]hex-6-yl-methyl]-2-(p-methylphenyl)-2-hydroxy-2-(N-methyl) phenylacetamide (Compound No. 18).
3. A pharmaceutical composition comprising a therapeutically effective amount of a compound as defined in claim 1 or 2 together with pharmaceutically acceptable carriers, excipients or diluents.
- 20 4. A method for treatment or prophylaxis of an animal or a human suffering from a disease or disorder of the respiratory, urinary and gastrointestinal systems, wherein the disease or disorder is mediated through muscarinic receptors, comprising administering to said animal or human, a therapeutically effective amount of a compound having the structure of Formula I,
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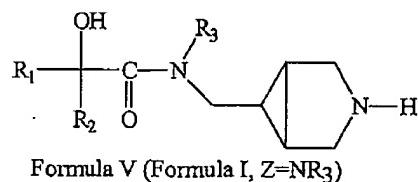
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its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, or metabolites, wherein

R<sub>1</sub> and R<sub>2</sub> are independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl or optionally substituted phenyl wherein optional substituent(s) is/are selected from C<sub>1</sub>-C<sub>3</sub> alkyl, C<sub>1</sub>-C<sub>3</sub> alkoxy or halogen;

Z represents oxygen or NR<sub>3</sub> wherein R<sub>3</sub> represents hydrogen or C<sub>1</sub>-C<sub>3</sub> alkyl.

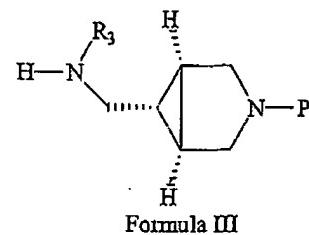
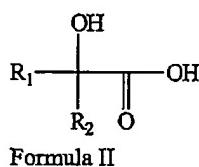
- 5. The method according to claim 4 wherein the disease or disorder is urinary incontinence, lower urinary tract symptoms (LUTS), bronchial asthma, chronic obstructive pulmonary disorders (COPD), pulmonary fibrosis, irritable bowel syndrome, obesity, diabetes or gastrointestinal hyperkinesis.
- 10. The method for treatment or prophylaxis of an animal or a human suffering from a disease or disorder of the respiratory, urinary and gastrointestinal systems, wherein the disease or disorder is mediated through muscarinic receptors, comprising administering to said animal or human, a therapeutically effective amount of the pharmaceutical composition according to claim 3.
- 15. The method according to claim 6 wherein the disease or disorder urinary incontinence, lower urinary tract symptoms (LUTS), bronchial asthma, chronic obstructive pulmonary disorders (COPD), pulmonary fibrosis, irritable bowel syndrome, obesity, diabetes or gastrointestinal hyperkinesis.
- 20. 8. A method of preparing a compound of Formula V,



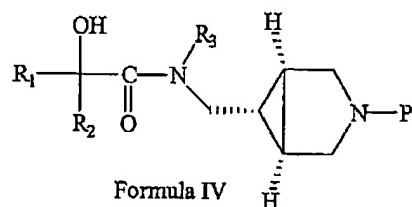
- 25. and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs or metabolites, wherein R<sub>1</sub> and R<sub>2</sub> are independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl or optionally substituted phenyl wherein optional substituent(s) is/are selected from C<sub>1</sub>-C<sub>3</sub> alkyl, C<sub>1</sub>-C<sub>3</sub> alkoxy or halogen;
- 30. R<sub>3</sub> represents hydrogen or C<sub>1</sub>-C<sub>3</sub> alkyl;

said method comprising:

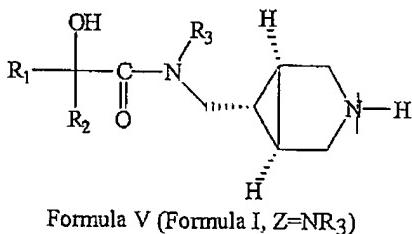
- (a) reacting a compound of Formula II with a compound of Formula III



to give a protected compound of Formula IV wherein R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> are as defined, and P is a protecting group for an amino group



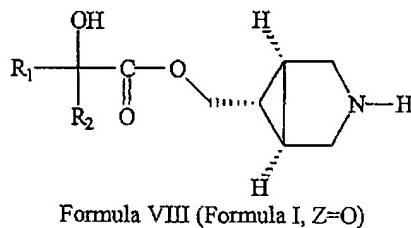
- (b) deprotecting the compound of Formula IV in the presence of a deprotecting agent to give compound of Formula V wherein R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> are as defined.
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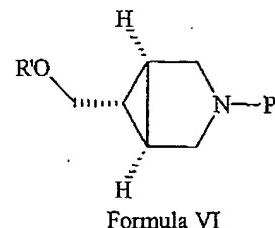
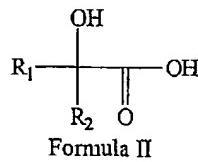
9. The method of claim 8, wherein P is any protecting group for an amino group and is selected from the group consisting of benzyl and t-butyloxycarbonyl groups.
10. The method of claim 8, wherein the reaction of a compound of Formula II with a compound of Formula III to give a compound of Formula IV is carried out in the presence of N-methylmorpholine and 1-hydroxybenzotriazole and a condensing agent which is selected from 1-(3-dimethyl amino propyl)-3-ethyl carbodiimide hydrochloride (EDC), 1,3-dicyclohexylcarbodiimide (DCC) or 1,8-diazabicyclo [5.4.0]undec-7-ene (DBU).
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11. The method of claim 8, wherein the reaction of a compound of Formula II with a compound of Formula III is carried out in a suitable polar aprotic solvent selected N,N-dimethylformamide, dimethyl sulfoxide, toluene, xylene and chloroform.
12. The method of claim 8, wherein the reaction of compound of Formula II with a compound of Formula III is carried out at 0-140°C.
- 5 13. The method of claim 8, wherein the deprotection of a compound of Formula IV is carried out with a deprotecting agent which is selected from palladium on carbon and hydrogen, ammonium formate and palladium on carbon, trifluoroacetic acid (TFA) or hydrochloric acid.
- 10 14. The method of claim 8, wherein the deprotection of a compound of Formula IV to give a compound of Formula V is carried out in a suitable organic solvent selected from methanol, ethanol, tetrahydrofuran or acetonitrile.
15. A method of preparing a compound of Formula VIII,



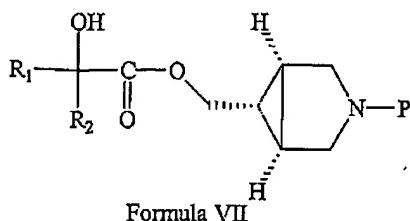
and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs or metabolites, wherein  
 20 R<sub>1</sub> and R<sub>2</sub> are independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl or optionally substituted phenyl wherein optional substituent(s) is/are selected from C<sub>1</sub>-C<sub>3</sub> alkyl, C<sub>1</sub>-C<sub>3</sub> alkoxy or halogen;  
 said method comprising:

- (a) reacting a compound of Formula II with a compound of Formula VI  
 25 (wherein R' is hydroxy protecting group selected of p-toluene sulfonyl or methane sulfonyl)



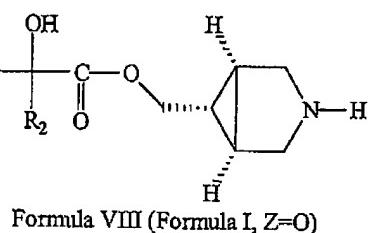
to give a protected compound of Formula VII wherein R<sub>1</sub> and R<sub>2</sub> are as defined, and P is a protecting group for an amino group

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- (b) deprotecting the compound of Formula VII in the presence of a deprotecting agent to give a compound of Formula VIII wherein R<sub>1</sub> and R<sub>2</sub> are as defined.



16. The method of claim 15, wherein P is any protecting group for an amino group and is selected from benzyl or t-butyloxycarbonyl groups.
17. The method of claim 15, wherein the reaction of a compound of Formula VI with a compound of Formula II to give a compound of Formula VII is carried out in the presence of a condensing agent which is selected from 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or 1,4-diazabicyclo[2.2.2]octane (DABCO).
18. The method of claim 15, wherein the reaction of a compound of Formula VI with a compound of Formula II is carried out in a solvent selected from benzene, toluene or xylene.
19. The method of claim 15, wherein the reaction of compound of Formula VI with a compound of Formula II is carried out at 0-140°C.
20. The method of claim 15, wherein the deprotection of a compound of Formula VII to give a compound of Formula VIII is carried out with a deprotecting agent which is selected from palladium on carbon and hydrogen gas or ammonium formate and palladium on carbon.

21. The method of claim 15, wherein the deprotection of a compound of Formula VII to give a compound of Formula VIII is carried out in a suitable organic solvent selected from methanol or ethanol.

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/IB2004/000008

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 7 C07D209/52 A61K31/403 A61P11/00 A61P13/00 A61P1/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, EPO-Internal

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 823 423 A (BANYU PHARMA CO LTD) 11 February 1998 (1998-02-11) cited in the application page 14, line 14 -page 16, line 24; claims 1,8,10,11 ---	1-21
A	EP 0 843 141 A (GEA WAERME UND UMWELTTECHNIK G) 20 May 1998 (1998-05-20) page 9, line 4 - line 26; claim 1; examples 1-13 ---	1-21
Y	WO 02/053564 A (ALMIRALL PRODESFRAMA AG ;BUIL ALBERO MARIA ANTONIA (ES); FERNANDEZ) 11 July 2002 (2002-07-11) page 38, line 26 -page 40; claims 1,33 --- -/-	1-21

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

## \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*&\* document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 May 2004	19/05/2004
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer  Schuemacher, A

## INTERNATIONAL SEARCH REPORT

International Application No

CT/IB2004/000008

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 02/04402 A (BANYU PHARMA CO LTD ; MATSUDA KENJI (JP); KURIHARA HIDEKI (JP); OGI) 17 January 2002 (2002-01-17) -& EP 1 302 458 A (BANYU PHARMACEUTICAL CO, LTD.) 16 April 2003 (2003-04-16) p.4, 1.18-30 page 67, line 1 - line 5; claims 22,27,29; example 26 ---	1-21
E	WO 2004/004629 A (RANBAXY LABORATORIES LIMITED, INDIA) 15 January 2004 (2004-01-15) the whole document ---	1-21
E	WO 2004/018422 A (RANBAXY LABORATORIES LIMITED, INDIA) 4 March 2004 (2004-03-04) the whole document ---	1-21

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/IB2004/000008

### ' Box II' Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  

Although claims 4-7 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2.  Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3.  Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple Inventions in this International application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the Invention first mentioned in the claims; it is covered by claims Nos.:

#### Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

CT/IB2004/000008

Patent document cited in search report	Publication date		Patent family member(s)	Publication date
EP 0823423	A 11-02-1998		AU 700837 B2 AU 5513996 A EP 0823423 A1 JP 2993124 B2 US 5750540 A CA 2218479 A1 WO 9633973 A1	14-01-1999 18-11-1996 11-02-1998 20-12-1999 12-05-1998 31-10-1996 31-10-1996
EP 0843141	A 20-05-1998		EP 0843141 A1 AT 166959 T DE 59600249 D1	20-05-1998 15-06-1998 30-07-1998
WO 02053564	A 11-07-2002		BR 0116624 A CA 2433128 A1 EE 200300312 A WO 02053564 A2 EP 1353919 A2 HU 0303524 A2 NO 20033002 A US 2004072863 A1	23-12-2003 11-07-2002 15-10-2003 11-07-2002 22-10-2003 28-01-2004 30-06-2003 15-04-2004
WO 0204402	A 17-01-2002		AU 7102701 A CA 2415468 A1 EP 1302458 A1 WO 0204402 A1 US 2003191316 A1	21-01-2002 10-01-2003 16-04-2003 17-01-2002 09-10-2003
WO 2004004629	A 15-01-2004		WO 2004004629 A2 WO 2004005252 A1	15-01-2004 15-01-2004
WO 2004018422	A 04-03-2004		WO 2004018422 A1	04-03-2004